A Prospective Evaluation of Entrainment Mapping as an Adjunct to New Generations High-Density Activation Mapping Systems of Left Atrial Tachycardias

Short title: Added value of entrainment in complex left ATs

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Abstract

Background. Identification of atrial tachycardia (AT) mechanism remains challenging.

Objective. We sought to investigate the added value of entrainment manoeuvres (EM) when using new high-density activation mapping (HDAM) technologies for the identification of complex left atrial tachycardias (AT).

Methods. Thirty-six consecutive complex ATs occurring after ablation of persistent AF were prospectively analysed. The AT mechanism was diagnosed in two steps by two experts: 1) based on HDAM only (Coherent, CARTO Biosense Webster) and 2) with additional analysis from EM.

Results. EM resulted in AF in one patient, which was excluded from the analysis. Ten of 11 single loop macro-reentry identified by HDAM were confirmed by EM. Only 4 of the 14 double loop macro-reentries identified by HDAM were confirmed by EM (in 10 patients, EM unmasked a passive activation of one of the visual circuits). One sole micro-reentry circuit identified by HDAM was confirmed by EM. A combination of macro- and micro-reentry circuits was visualized in three ATs using HDAM. However, EM revealed a passive activation of the visual macro-reentrant loop in 2 of these 3 cases. By using HDAM in 6 out of 35 ATs (17%), no univocal mechanism could be identified whereas EM finally enabled the diagnosis of five micro-reentry circuits and one macro-reentrant AT. All of the diagnoses made from EM on top of HDAM were confirmed by ablation.

Conclusion. Entrainment manoeuvres are still useful during mapping of complex left atrial tachycardia, mostly to differentiate active from passive macro-reentrant loops and to demonstrate micro-reentry circuits.

Keywords: Atrial tachycardia, Entrainment, Local activation time, High-density activation mapping, Catheter ablation

Introduction

Complex left atrial tachycardia (AT) are frequent after ablation of persistent AF [1,2]. New generation activation mapping systems, sometimes using multi-electrode mapping catheters and automatic annotation of local activation time (LAT), have shown promising results[3,4]. Recently, a novel mapping algorithm (Coherent, CARTO Biosense Webster) has been demonstrated to have higher accuracy in identifying complex scar-related macro-reentrant circuits, as it integrates information about conduction velocities[5]. In recent studies, authors did not systematically use entrainment manoeuvres to confirm the diagnosis[6,7]. Nonetheless, in case of very diseased left atrium (LA) (spontaneously or after extensive ablation), the interpretation of these high-density activation maps (HDAM) can remain challenging.

On the other hand, even when using new generation HDAM technologies, entrainment mapping (EM) has still shown its usefulness during complex right AT, mostly to discriminate active and bystander circuits[8]. However, the exact added value of EM has not yet been investigated yet during complex left AT.

In this prospective single centre study, we sought to investigate whether EM is valuable even when the newest technologies for the identification of complex left ATs after persistent AF ablation are being used.

Methods

Study population

From March 2018 to February 2019, patients undergoing catheter ablation for left AT were prospectively included in the study, only if previous persistent AF ablation procedures were considered as “complex”. The previous ablation procedures were considered as complex if, in addition to pulmonary vein isolation, a set of two ablation lines (roof, mitral isthmus)[9] and additional substrate ablation (CFAE ablation) had been performed during the first procedure. Patients' informed consent and a detailed case-report form of the procedure were collected in a local database. The study is in accordance with the Declaration of Helsinki and has been approved by the local Ethical Committee.

Study design

AT maps were prospectively analysed by two expert electrophysiologists during the ablation procedure. For each AT, they were asked to make a diagnosis of the mechanism following a two-steps procedure: 1) firstly by looking at the HDAM (blinded to EM results) and with electrogram (EGM) analysis and then secondly 2) with additional analysis from EM added on the HDAM. For the two steps, they had to reach a consensus on the AT mechanism and its precise location/circuit. The diagnosis was considered correct if the ablation led to AT termination (to sinus rhythm or to another AT as suggested by a different cycle length/activation pattern).

AT mechanism definitions

Macro-reentries were defined as roof dependent circuits when turning around the right pulmonary veins (RPV) or left pulmonary veins (LPV), or perimitral when turning around the mitral annulus. A double loop AT was defined as two simultaneous macro-reentry circuits with a common isthmus.

AT was defined as a micro-reentry circuit in the case of centrifugal activation from one atrial segment with at least 75% of the AT cycle length within the earliest region [10].

Procedure

All procedures were performed by four different operators, under general anaesthesia, and under direct anticoagulants (last dose ≤24 hrs before procedure) or uninterrupted warfarin.

Antiarrhythmic drugs were withdrawn 24 hrs before the procedure. No antiarrhythmic medication was administered during the procedure. An oesophageal temperature monitoring probe (SensiTherm™, St. Jude Medical Inc., Abbott, Chicago, IL, USA) was placed at the discretion of the operator. Intravenous heparin was administered after femoral vein access to achieve an activated clotting time >350 sec. A decapolar coronary sinus (CS) catheter was introduced via the right femoral vein, and a double trans-septal puncture was performed with conventional long sheaths (SL0, St. JudeMedical Inc., Abbott, Chicago, IL, USA). A multi-electrode mapping catheter (PENTARAY®, Biosense Webster Inc., Irvine, CA, USA) and an open-tip irrigated radiofrequency (RF) catheter (8 Fr) with tip-integrated contact force (CF) sensor (Thermocool SmartTouch®, Biosense-Webster Inc., Irvine, CA, USA) were positioned in the LA. Then, calibration of the CF catheter, respiratory gating, and acquisition of 3D geometry of the LA (Carto System, Biosense Webster Inc., Irvine, CA, USA) were performed.

High Density Activation mapping

The Coherent module (CARTO®, Biosense Webster Inc., Irvine, CA, USA) has been previously described[5]. Basically, the new algorithm takes into account three descriptors, i.e. LAT value, conduction vector, and the probability of non-conductivity, that are used to generate an integrative activation map displayed as a vector map. This algorithm then identifies the optimal conduction mechanism, considering physiological barriers manifested by scar and double potentials. Colouring is based on the best fit solution of all LAT values of the map identifying the conduction mechanism.

Entrainment mapping

Entrainment was performed at predefined LA sites around both pulmonary vein (PV) circles and the mitral annulus, as well as at sites located in proximity to the observed circuits, at a cycle length of 10 ms less than the tachycardia cycle length (TCL). A post-pacing interval (PPI), measured from the stimulation artefact to the return atrial EGM on the pacing catheter and not exceeding the tachycardia TCL by more than 30 ms in three opposite atrial locations corroborated the diagnosis of macro-reentry. A colour code was used to illustrate the PPI results: a green point corresponded to a PPI-TCL < 30 ms, a yellow point to a PPI-TCL between 30 and 50 ms and a black point to a PPI-TCL > 50 ms.

If PPI-TCL was unexpectedly long based upon the diagnosis from the HDAM, the entrainment manoeuvre was repeated to ensure correct capture, after having checked the TCL and activation pattern in order to exclude any changes in the AT mechanism.

Radiofrequency Ablation

RF ablation (20- 40 Watts, 30 cc irrigation rate) was performed depending on the AT mechanism and the ablation lines that had previously been performed. In the case of a micro-reentry circuit, ablation was focused mostly on the earliest area where local electrogram filled >75% of the TCL. The diagnosis of the AT mechanism was considered correct if the AT terminated during radiofrequency ablation (to sinus rhythm or to another AT). In every patient, the operators aimed to reach the non-inducibility of any AT at the end of the procedure.

Statistical analysis

Continuous variables are presented as mean±SD, or median with interquartile range (IQR). Categorical variables are presented as percentages (%) and counts. Two-group comparisons of continuous variables were performed by Student's t-tests if normally distributed or with Wilcoxon Rank-Sum tests if the normality assumption was violated according to Shapiro-Wilk tests. Two-tailed p-values <0.05 were considered to indicate statistical significance. Statistical analyses were performed using SPSS 25.0 (IBM, Armonk, New York, USA).

Results

<u>Study population and procedural characteristics</u>

Sixty-one consecutive patients underwent AT ablation during the index period. Thirty-six out of 72 AT in 32 patients fulfilled complex AT criteria as mentioned above. In one patient, EM resulted in AF after HDAM. In this patient, a direct current cardioversion (DCCV) was carried out, however an AT could not be induced anymore and the patient was excluded.

Clinical characteristics of the remaining 31 patients (35 ATs) are shown in Table 1. The majority of patients (63%) were male with a mean age of 69±11 years and a mean CHA_2DS_2VASc of 2±1. The median number of previous ablations was 1 (IQR 1-2).

There was a median of 1031 points (IQR 830 – 1625) per map and a mean number of 8±4 pacing sites during EM.

<u>Accuracy of HDAM and added value of EM</u>

Macro-reentries (single or double loop)

Eleven single loop macro-reentries were identified by HDAM (31%): seven roof circuits (four around RPVs and three around LPVs), and four perimitral circuits (figure 1 and 2). EM confirmed the mechanism and the circuit in all cases except for one AT where EM enabled the diagnosis of a perimitral circuit with a breakthrough at the left atrial appendage (LAA) base through the vein of Marshall, whereas analysis of HDAM misclassified it as a roof circuit around LPVs. In total, HDAM established a correct diagnosis in 10 out of 11 (91%) maps showing single loop macro-reentry.

Fourteen double loop ATs were identified by HDAM (40%): three roof dependent macro-reentrant ATs with two simultaneous circuits around both right and left PVs, and 11 simultaneous perimitral and roof circuits (four around RPVs and seven around LPVs). With EM, only 4 out of 14 double loop ATs (28.5%) were confirmed, while in the other 10 cases, EM unmasked a passive activation of one visual circuit (figure 3 and 4). For these 10 ATs with a passive activation of a visual circuit, the final diagnosis was thus single loop macro-reentries: five roof circuits (three around the RPVs and two around the left PVs) and five perimitral circuits.

Micro-reentry circuits

One sole micro-reentry circuit (located at the anterior LA wall) was identified by HDAM (3%) and then confirmed by EM.

Combination of macro- and micro-reentry circuits

HDAM showed a combination of a macro- and micro-reentry circuits in three ATs (9%): two perimitral circuits in combination with an anterior micro-reentry, and one roof circuit around RPVs in combination with a posterior micro-reentry.

In the first two cases, EM revealed a passive activation of the visual perimitral circuit while the anterior micro-reentry circuit was confirmed. Ablation of the anterior micro-reentry resulted in sinus rhythm restoration.

In the third case, EM confirmed that both macro- and micro-reentry circuits were active.

No diagnosis possible from troubleshooting HDAM

In the remaining 6 out of 35 ATs (17%), it was not possible to depict at least one univocal AT mechanism using HDAM alone. In these cases, EM finally enabled the diagnosis of five micro-reentry circuits (two located at the anterior wall, one at the septum, one at the roof and one at the base of the appendage) (figure 5) and one roof dependant macro-reentrant AT turning around LPVs.

AT final characteristics as confirmed by ablation

AT characteristics are summarized in Table 2.

The median AT TCL was 275 ms (IQR 240-320). Ablation converted AT to sinus rhythm in 23 patients (66%) and to another AT in 12 (34%) cases. EM on top of HDAM enabled the correct AT diagnosis (location and circuit) in all cases, as confirmed by ablation (figure 1).

There were finally 22 single loop macro-reentries (63%) (figure 2): 10 perimitral circuits (four counter-clockwise and five clockwise) for which a mitral line was conducted; and 12 roof dependant circuits for which a roof line was performed [(seven around RPVs (four counter-clockwise and three clockwise) and five around LPVs (two counter-clockwise and three clockwise)]. In 5 out of 10 patients with a putative double loop at HDAM but not confirmed by EM, ablation was performed at a common isthmus (mitral line or roof line), which resulted in sinus rhythm restoration in all cases. In the remaining five patients, ablation of the active circuit resulted in AT transformation to the initially passive loop in three patients and in sinus rhythm restoration in two patients.

Four double loop macro-reentries (11%) were diagnosed: one double roof circuit around RPVs and LPVs for which ablation at the roof was performed, and three simultaneous perimitral and roof circuits (two around LPVs and one around RPVs) for which ablation was first performed at the roof line and then at the mitral line.

Eight micro-reentry circuits (23%) were diagnosed: five located at the anterior wall, one at the septum, one at the roof and one at the base of the appendage.

In one case (3%), there was a combination of one macro-reentry around RPVs and one micro-reentry around a posterior scar area.

Discussion

This study shows the importance of EM for accurate identification of complex left atrial tachycardias occurring after persistent AF ablation, on top of HDAM. This was mostly true for micro-reentry circuits, which were not adequately depicted by HDAM and for differentiating active from passive macro-reentries in the case of double loop AT.

New generation activation mapping: pro's and con's

Accurate activation mapping is crucial to understand AT mechanism and location. There has been a lot of evolution concerning the different algorithms and systems, with improving results. The Rhythmia® system (Boston Scientific, Natick, MA, USA) has been shown to increase mapping accuracy and to correctly identify the critical isthmus of ATs, particularly in very diseased atria with low voltage and slow conducting area [11,6,12]. The Coherent® mapping algorithm (Biosense Webster Inc, Irvine, CA, USA) has also been associated with promising results as it enabled accurate identification of the AT mechanism in >90% of cases as compared to 66.7% using standard algorithm in a recent study[5].

However, despite these latest improvements, limitations of HDAM persist in the cases of complex AT[6]. Indeed, automatic EGM annotations are sometimes inadequate in the case of low voltage fractionated multicomponent electrograms. Another potential limitation of HDAM is that it is sometimes impossible to discriminate active from passive activation particularly in the case of an activation pattern filling the AT cycle length. Finally, the mapping window is arbitrarily defined and may miss focal mechanisms.

Our study highlighted these problems encountered during HDAM alone. First of all, “false” double loop macro-reentrant ATs were frequently visualized with HDAM; however they were only confirmed by EM in few cases. Secondly, the performance of HDAM for diagnosing micro-reentrant ATs was poor. This was mostly due to the problems encountered by the system to correctly annotate multicomponent and long duration fractionated EGMs in micro-reentrant ATs as well as to correctly represent a very small micro-reentry circuit with colour coding. Furthermore, micro-reentry circuits often generate passive activations around the atrium, which can mimic larger macro-reentrant ATs and render difficult diagnosing.

How to overcome limitations of standard activation mapping in complex substrates and the role of EM

EM is a pivotal electrophysiological technique to identify arrhythmia mechanisms as well as to define components of the reentrant circuit[13,14]. In a previous study, EM has been integrated in 3D colour coded entrainment maps, without added activation mapping [15]. Using this strategy in 39 ATs, authors were able to visualize the complete macro-reentrant circuit and to apply strategic linear lesions instead of targeting the slow conduction area, resulting in 100% procedural success and long-term freedom from recurrence in 88%.

However, entrainment mapping alone has limitations: 1) EM can change or terminate the arrhythmia[16], 2) in low voltage regions, capture is not always possible and sometimes it may be difficult to identify the narrow isthmus as well as delineate complex circuits in patients with abnormal atrial anatomy and regions of scar, 3) decremental conduction during pacing may increase the post-pacing intervals, leading to misclassify a point as far from the circuit [17].

Therefore, EM is mostly used on top of activation mapping to confirm or reject a potential diagnosis. Nonetheless, in the present study, EM altered AT in only 1 out of 36 cases (3%). As already shown by a previous study, this evidences the relative safety of entrainment manoeuvres when performed correctly[16].

The combination of standard activation mapping with EM has been already associated with good results[11,1] but it was never really tested using next generation HDAM systems in the LA. In the RA, a study by Pathik et al. on right atrial ATs clarified that HDAM often shows visual reentrant circuits that are only bystanders and not part of the circuit and entrainment remains therefore central in confirming the active components of the atrial macro-reentrant circuits[8].

Clinical implications

Despite the recent improvement of HDAM technologies, we are still far from achieving the correct diagnosis in all cases with this technology, especially in complex left ATs after persistent atrial fibrillation ablation. Therefore, EM still represents a crucial additional tool to increase the diagnostic accuracy. HDAM is reliable in identifying single loop macro-reentrant circuits, but often shows double loop AT and in this case, EM will help in differentiating a passive from an active activation of one of both loops. In the case of a passive visual circuit, ablation of the active AT results in AT transformation to the initial passive circuit in a significant amount of patients, suggesting that ablation of the passive visual circuit in addition to the active one could be of interest; however, this obviously requires confirmation. Finally, EM is also crucial in the diagnostic process of micro-reentry circuits that are often missed by HDAM.

<u>*Limitations*</u>

This study concerns a relatively small cohort of patients and although it was prospective, this was a monocentric study. Furthermore, only one mapping system was used and results could be different with other technologies. Finally, fusion in P-Wave morphology at different pacing rates was not systematically used and this could have led to some errors, even if, in the case of atrial tachycardia, small changes in the P wave morphology are often difficult to evidence.

Conclusion

Entrainment manoeuvres are still useful during mapping of complex left atrial tachycardia, mostly to differentiate active from passive macro-reentrant loops and to demonstrate micro-reentry circuits.

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Figure Legend

Figure 1

Diagnostic flowchart of the ATs' mechanism as suggested by HDAM alone (left column), HDAM and EM (middle column) and as confirmed by ablation (right column)

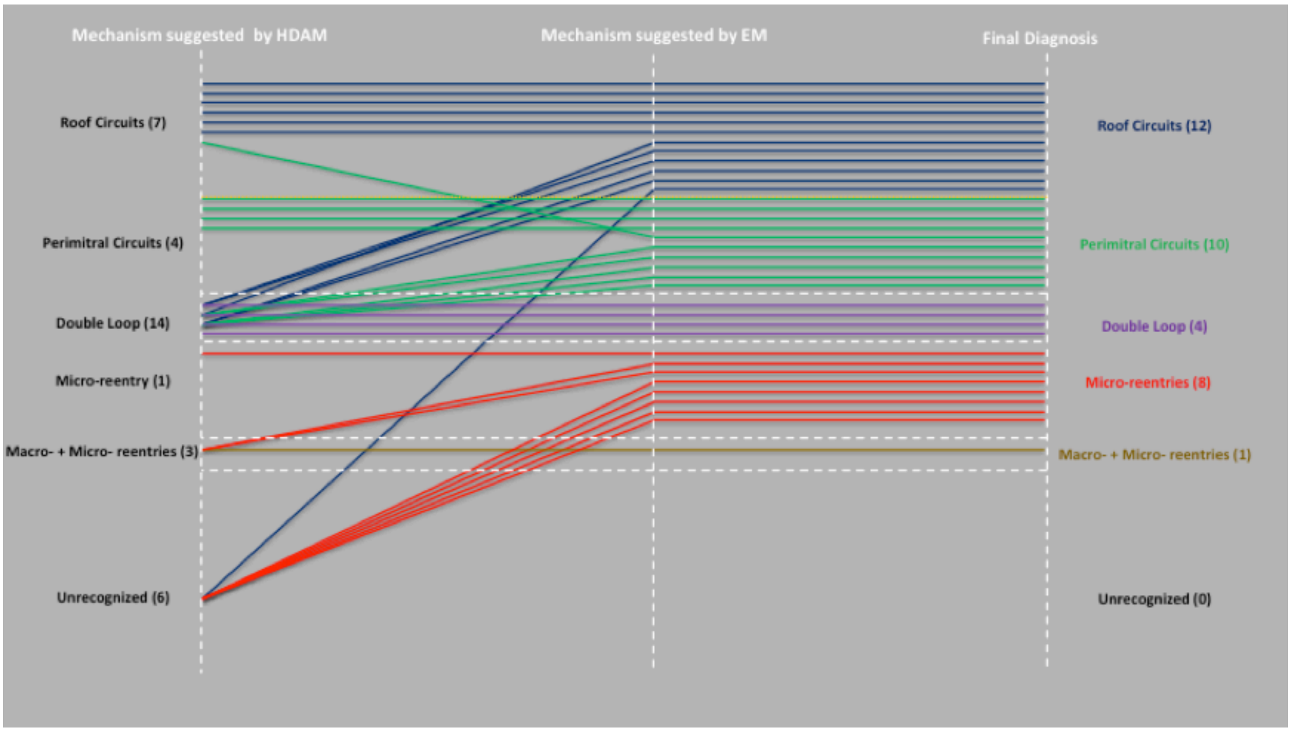
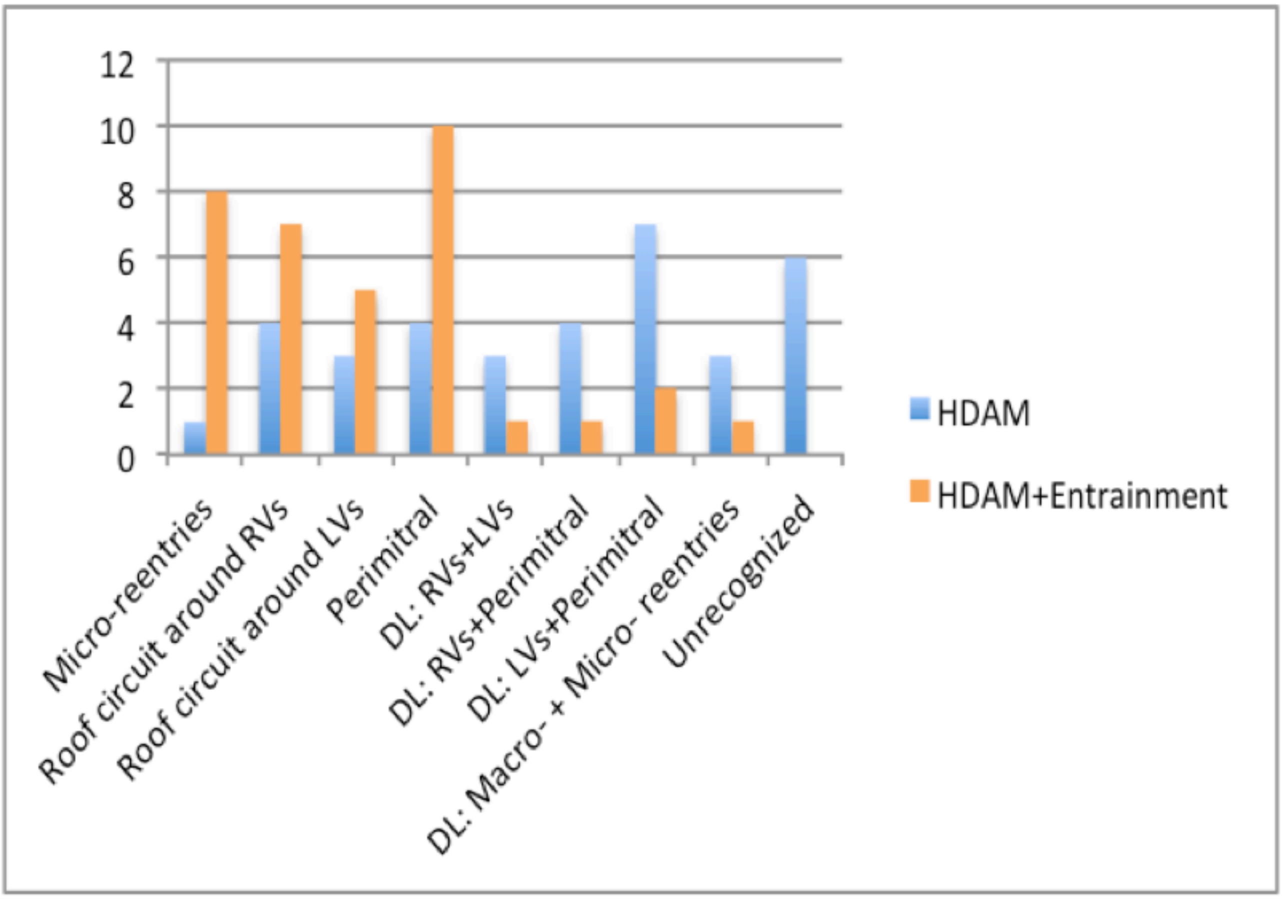


Figure 2

Distributions of ATs mechanisms based on high-density activation mapping (HDAM) and on HDAM + entrainment manoeuvres (EM).

DL: double loop; RVs: right veins; LVs: left veins



AT Mechanism	HDAM	HDAM+Entrainment
Micro-reentries	1	8
Roof circuit around RVs	4	7
Roof circuit around LVs	3	5
Perimitral	4	10
DL: RVs+LVs	3	1
DL: RVs+Perimitral	4	1
DL: LVs+Perimitral	7	2
DL: Macro- + Micro- reentries	3	1
Unrecognized	6	0

Figure 3

In panel A (left: antero-posterior view; right: adapted postero-anterior view), a double loop pattern was suggested by HDAM: one clockwise perimitral circuit and one roof circuit turning counter-clockwise around the left veins (LVs). However, EM showed a long PPI-TCL (black dot) on the roof, which suggested a passive activation around the LVs. Ablation at the mitral isthmus restored sinus rhythm.

In panel B (left: antero-posterior view; right: adapted postero-anterior view), HDAM suggested a double loop pattern: one counter-clockwise perimitral circuit and one roof circuit turning clockwise around LVs. EM confirmed the diagnosis (green dots, perfect PPI-TCL). A roof line was drawn, resulting in a single perimitral pattern with the same AT cycle length. An additional mitral line restored sinus rhythm.

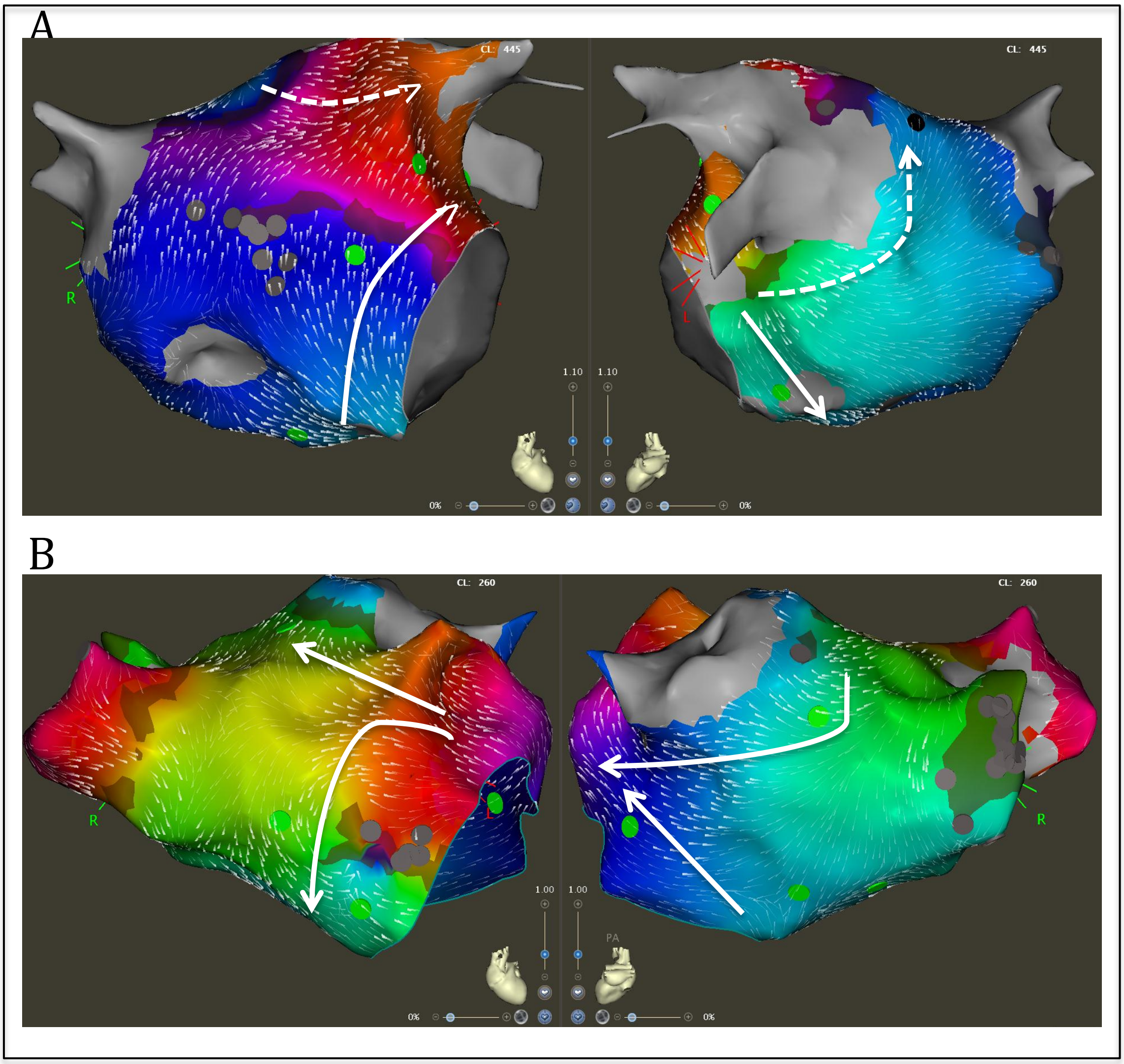

A
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Figure 4

Double loop AT. In panel A two circuits, one perimitral and one turning around left veins, are evident. These macro-reentries suggested by HDAM were confirmed by good PPI (green points) along the roof and the mitral annulus. The roof line ablation didn't stop or change the AT cycle length, however, as shown in panel B the PPI at both sides of the line were bad, whereas before ablation were good. Further ablation at the mitral isthmus stopped the AT.

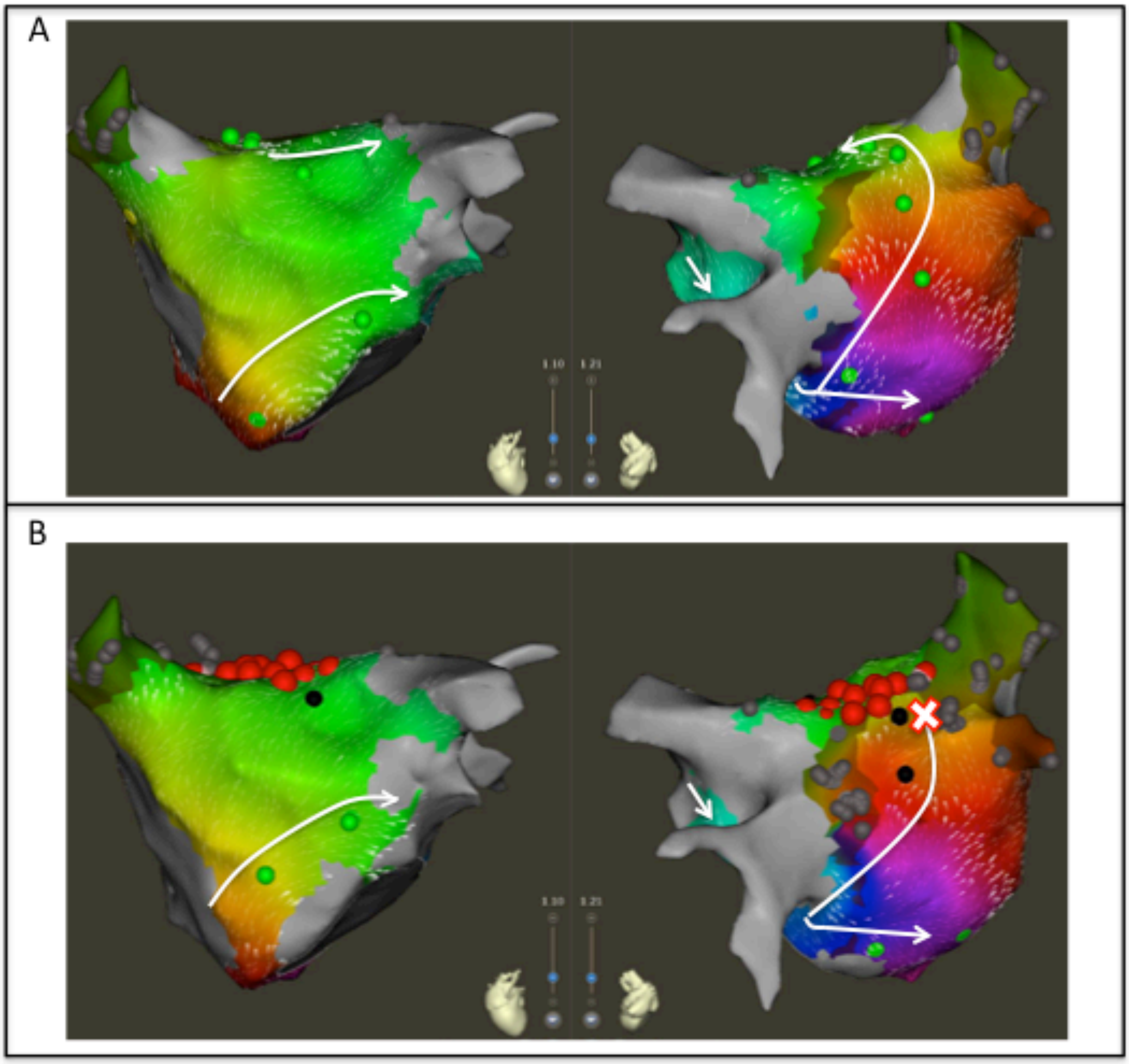

Figure 5

HDAM suggested a reentry around scar tissue at the anterior wall (left: antero-posterior view; right: adapted postero-anterior view). A perimitral pattern could also not be excluded (dotted lines). However, PPI-TCL was long all around the supposed anterior reentry and around the mitral annulus (black and yellow dots). EM were surprisingly good at the ridge between the left superior pulmonary vein and left atrial appendage, where a very fractionated EGM covering 79% of the tachycardia cycle length was evidenced (pink dots), confirming the presence of a micro-reentry. Ablation at this spot restored sinus rhythm within one second.